

Amendment to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Currently amended) A composition comprising:
an siRNA or shRNA molecule targeted to a target transcript of a respiratory virus,
which molecule comprises wherein the target transcript is an agent-specific transcript,
which transcript is involved in infection by or replication of an infectious agent (a) a first
single-stranded RNA molecule consisting of a sequence that is homologous to highly
conserved region of the target transcript among a plurality of variants of the virus and
comprises at least 15 consecutive nucleotides, (b) a second single-stranded molecule
that comprises a region that is complementary to the first strand, and (c) an RNA duplex
formed by the first and second RNA molecules hybridizing together,
wherein the siRNA or shRNA molecule inhibits production of the virus by at least 2 fold,
relative to the level that would be present in the absence of the siRNA or shRNA
molecule, in cells infected by the virus.
2. (Currently amended) The composition of claim 1, wherein:
the respiratory virus infectious agent is an agent whose genome comprises
multiple independent nucleic acid molecules.
3. (Original) The composition of claim 2, wherein:
the nucleic acid molecules are RNA.
4. (Original) The composition of claim 2, wherein:
the RNA molecules are single-stranded.
5. (Currently amended) The composition of claim 1, wherein:
~~multiple variants of the infectious agent exist and wherein~~ the respiratory virus
agent is capable of undergoing genetic reassortment.

6. (Currently amended) The composition of claim 1, wherein:
~~multiple variants of the infectious agent exist and wherein the siRNA or shRNA molecule comprises a sequence duplex region whose antisense strand or antisense portion is perfectly complementary to a portion of a target mRNA, which portion that is at least 10 nucleotides in length and is highly conserved among the [[a]] plurality of variants.~~
7. (Currently amended) The composition of claim 6, wherein:
~~multiple variants of the infectious agent exist and wherein the siRNA or shRNA molecule comprises a sequence duplex region whose antisense strand or antisense portion is perfectly complementary to a portion of a target mRNA, which portion that is at least 12 nucleotides in length and is highly conserved among the [[a]] plurality of variants.~~
8. (Currently amended) The composition of claim 6, wherein:
~~multiple variants of the infectious agent exist and wherein the siRNA or shRNA molecule comprises a sequence duplex region whose antisense strand or antisense portion is perfectly complementary to a portion of a target mRNA, which portion that is at least 15 nucleotides in length and is highly conserved among the [[a]] plurality of variants.~~
9. (Currently amended) The composition of claim 6, wherein:
~~multiple variants of the infectious agent exist and wherein the siRNA or shRNA molecule comprises a sequence duplex region whose antisense strand or antisense portion is perfectly complementary to a portion of a target mRNA, which portion that is at least 17 nucleotides in length and is highly conserved among the [[a]] plurality of variants.~~
10. (Currently amended) The composition of claim 6, wherein:
~~multiple variants of the infectious agent exist and wherein the siRNA or shRNA molecule comprises a sequence duplex region whose antisense strand or antisense portion is perfectly complementary to a portion of a target mRNA, which portion that is at least 19 nucleotides in length and is highly conserved among the [[a]] plurality of variants.~~
11. (Currently amended) The composition of claim 8, wherein:
~~the sequence a portion is highly conserved among variants if it is identical among the different variants.~~

12. (Currently amended) The composition of claim 8, wherein
~~the sequence a portion is highly conserved among variants~~ if it varies by at most one nucleotide between different variants.
13. (Currently amended) The composition of claim 8, wherein:
~~the sequence a portion is highly conserved among variants~~ if it varies by at most two nucleotides between different variants.
14. (Currently amended) The composition of claim 8 wherein:
~~the sequence a portion~~ is highly conserved among at least 5 variants.
15. (Currently amended) The composition of claim 8, wherein:
~~the sequence a portion~~ is highly conserved among at least 10 variants.
16. (Currently amended) The composition of claim 8, wherein:
~~the sequence a portion~~ is highly conserved among at least 15 variants.
17. (Currently amended) The composition of claim 8, wherein:
~~the sequence a portion~~ is highly conserved among at least 20 variants.
18. (Currently amended) The composition of claim 1, wherein:
~~the respiratory virus the infectious agent~~ infects respiratory epithelial cells.
19. (Currently amended) The composition of claim 1, wherein:
~~the respiratory virus the infectious agent~~ is an influenza virus.
20. (Original) The composition of claim 19, wherein:
the influenza virus is an influenza A virus.
21. (Withdrawn) The composition of claim 19, wherein:
the influenza virus is an influenza B virus.
22. (Currently amended) The composition of claim 1, wherein:
~~the respiratory virus the infectious agent~~ inhibits host cell mRNA translation.
- 23-25. (Canceled)

27. (Currently amended) The composition of claim 1, wherein:
the respiratory virus ~~the infectious agent~~ infects a host cell and the siRNA or shRNA is present at a level sufficient to inhibit production of the virus agent by a host cell by at least about 100 fold.
28. (Currently amended) The composition of claim 1, wherein:
the respiratory virus ~~the infectious agent~~ infects a host cell and the siRNA or shRNA is present at a level sufficient to inhibit production of the virus agent by a host cell by at least about 200 fold.
29. (Withdrawn) The composition of claim 1, wherein:
the target transcript encodes a subunit of a viral RNA polymerase.
30. (Withdrawn) The composition of claim 1, wherein:
the target transcript encodes a hemagglutinin or a neuraminidase.
31. (Currently amended) The composition of claim 1, wherein:
the respiratory virus ~~the infectious agent~~ is an influenza virus and the target transcript encodes a protein selected from the group consisting of hemagglutinin, neuraminidase, membrane protein 1, membrane protein 2, nonstructural protein 1, nonstructural protein 2, polymerase protein PB1, polymerase protein PB2, polymerase protein PA, polymerase protein NP.
32. (Currently amended) The composition of claim 1, wherein:
the siRNA or shRNA is present at a level sufficient to inhibit replication of the respiratory virus ~~the infectious agent~~.
33. (Currently amended) The composition of claim 1, wherein:
the duplex ~~the siRNA or shRNA~~ comprises a base-paired region at least 15 nucleotides long.
34. (Currently amended) The composition of claim 1, wherein:
the duplex ~~the siRNA or shRNA~~ comprises a base-paired region approximately 19 nucleotides long.

35. (Currently amended) The composition of claim 1, wherein:

~~the duplex~~ ~~the siRNA or shRNA~~ comprises a base-paired region at least 15 nucleotides long and at least one single-stranded 3 prime overhang.

36-38. (Canceled)

39. (Currently amended) The composition of claim 1, wherein:

~~the first strand~~ ~~siRNA or shRNA~~ comprises a core duplex region, wherein the ~~sequence of the sense strand or portion of the core duplex region~~ comprises at least 10 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68.

40. (Currently amended) The composition of claim 1, wherein:

~~the first strand~~ ~~siRNA or shRNA~~ comprises a core duplex region, wherein the ~~sequence of the sense strand or portion of the core duplex region~~ comprises at least 12 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68.

41. (Currently amended) The composition of claim 1, wherein:

~~the first strand~~ ~~siRNA or shRNA~~ comprises a core duplex region, wherein the ~~sequence of the sense strand or portion of the core duplex region~~ comprises at least 15 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68.

42. (Currently amended) The composition of claim 1, wherein:

~~the first strand~~ ~~siRNA or shRNA~~ comprises a core duplex region, wherein the ~~sequence of the sense strand or portion of the core duplex region~~ comprises at least 17 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68.

43. (Currently amended) The composition of claim 1, wherein:

~~the first strand~~ ~~siRNA or shRNA~~ comprises a core duplex region, wherein the ~~sequence of the sense strand or portion of the core duplex region~~ comprises at least 19

consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68.

44. (Currently amended) The composition of claim 1, wherein:

~~the first strand siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 10 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68, with the proviso that either one or two nucleotides among the 10 consecutive nucleotides may differ from that sequence.~~

45. (Currently amended) The composition of claim 1, wherein:

~~the first strand siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 12 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68, with the proviso that either one or two nucleotides among the 12 consecutive nucleotides may differ from that sequence.~~

46. (Currently amended) The composition of claim 1, wherein:

~~the first strand siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 15 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68, with the proviso that either one or two nucleotides among the 15 consecutive nucleotides may differ from that sequence.~~

47. (Currently amended) The composition of claim 1, wherein:

~~the first strand siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 17 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68, with the proviso that either one or two nucleotides among the 17 consecutive nucleotides may differ from that sequence.~~

48. (Currently amended) The composition of claim 1, wherein:

~~the first strand siRNA or shRNA comprises a core duplex region, wherein the~~

sequence of the sense strand or portion of the core duplex region comprises at least 19 consecutive nucleotides as set forth in nucleotides 3 through 21 of the sequence presented in any of SEQ ID NOS: 1 through 68, with the proviso that either one or two nucleotides among the 19 consecutive nucleotides may differ from that sequence.

49. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 10 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268.

50. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 12 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268.

51. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 15 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268.

52. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 17 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of

SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268.

53. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 19 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268.

54. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 10 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268, with the proviso that either one or two nucleotides among the 10 consecutive nucleotides may differ from that sequence.

55. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 12 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268, with the proviso that either one or two nucleotides among the 12 consecutive nucleotides may differ from that sequence.

56. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 15 consecutive

nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268, with the proviso that either one or two nucleotides among the 15 consecutive nucleotides may differ from that sequence.

57. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 17 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268, with the proviso that either one or two nucleotides among the 17 consecutive nucleotides may differ from that sequence.

58. (Withdrawn) The composition of claim 1, wherein:

the siRNA or shRNA comprises a core duplex region, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 19 consecutive nucleotides as set forth in nucleotides 1 through 19 of the sequence presented in any of SEQ ID NOS: 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, or 268, with the proviso that either one or two nucleotides among the 19 consecutive nucleotides may differ from that sequence.

59. (Withdrawn) The composition of claim 1, wherein the siRNA or shRNA comprises sense and antisense strands or portions whose sequences comprise sequences given by nucleotides 1 – 19 of SEQ ID NOS: 77 and 78 respectively, with, optionally, a 3' overhang on one or both sequences.

60. (Withdrawn) The composition of claim 1, wherein the siRNA or shRNA comprises sense and antisense portions whose sequences comprise sequences given by nucleotides 1 – 19 of SEQ ID NOS: 71 and 72 respectively, with, optionally, a 3' overhang on one or both sequences.

61. (Withdrawn) The composition of claim 1, wherein the siRNA or shRNA comprises sense and antisense portions whose sequences comprise sequences given by nucleotides 1 – 19 of SEQ ID NOS: 83 and 84 respectively, with, optionally, a 3' overhang on one or both sequences.
62. (Withdrawn) The composition of claim 1, wherein the siRNA or shRNA comprises sense and antisense portions whose sequences comprise sequences given by nucleotides 1 – 19 of SEQ ID NOS: 89 and 90 respectively, with, optionally, a 3' overhang on one or both sequences.
63. (Withdrawn) The composition of claim 1, wherein the siRNA or shRNA comprises sense and antisense portions whose sequences comprise sequences given by nucleotides 1 – 19 of SEQ ID NOS: 91 and 92 respectively, with, optionally, a 3' overhang on one or both sequences.
64. (Currently amended) The composition of claim 1, wherein ~~the duplex~~ the siRNA or shRNA comprises ~~sense and antisense portions whose sequences comprise~~ sequences given by nucleotides 1 – 19 of SEQ ID NOS: 93 and 94 respectively, with, optionally, a 3' overhang on one or both sequences.
65. (Currently amended) The composition of claim 1, wherein ~~the duplex~~ the siRNA or shRNA comprises ~~sense and antisense portions whose sequences comprise~~ sequences given by nucleotides 1 – 20 of SEQ ID NOS: 188 and 189 respectively, with, optionally, a 3' overhang on one or both sequences.
66. (Currently amended) The composition of claim 1, wherein the siRNA or shRNA ~~comprises a duplex~~ is a portion selected from the group consisting of duplex portions of: NP-1496, NP-1496a, PA-2087, PB1-2257, PB1-129, PB2-2240, M-37, or M-598 or a variant of any of the foregoing, which variant differs by at most one nucleotide from the corresponding siRNA.
67. (Currently amended) The composition of claim 66, wherein the siRNA or shRNA duplex ~~portion~~ is identical to the duplex portion of NP-1496.

68. (Currently amended) The composition of claim 66, wherein the siRNA or shRNA duplex ~~portion~~ is identical to the duplex portion of NP-1496a.
69. (Currently amended) The composition of claim 1, wherein the first sense strand ~~or portion of the siRNA or shRNA~~ has a sequence selected from the group consisting of: the first 19 nucleotides of SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 93; SEQ ID NO: 95; SEQ ID NO: 99, and SEQ ID NO: 188, reading in a 5' to 3' direction.
70. (Currently amended) ~~The composition~~ An analog of the siRNA or shRNA of claim 1, wherein first or second strand ~~the analog differs from the siRNA or shRNA in that it~~ contains at least one nucleotide modification.
71. (Currently amended) The composition analog of claim 70, wherein:
the modification results in increased stability of the siRNA, enhances absorption of the siRNA, enhances cellular entry of the siRNA, or any combination of the foregoing.
72. (Currently amended) The composition analog of claim 70, wherein:
the modification modifies a base, a sugar, or an internucleoside linkage.
73. (Currently amended) The composition analog of claim 70, wherein:
the modification is not a nucleotide 2' modification.
74. (Currently amended) The composition analog of claim 70, wherein:
the modification is a nucleotide 2' modification.
75. (Currently amended) ~~The composition~~ An analog of the siRNA or shRNA of claim 1, wherein:
~~the analog differs from the siRNA in that~~ at least one ribonucleotide of the first or second strand is replaced by a deoxyribonucleotide.
76. (Currently amended) The [[A]] composition of claim 1, comprising a plurality of first strands and second strands ~~single stranded RNAs~~ which, when hybridized to each other, form duplexes ~~the composition of claim 1~~.

77. (Currently amended) The composition of claim 76, wherein:
the first and second strands ~~single-stranded RNAs~~ range in length between approximately 21 and 23 nucleotides, inclusive.
78. (Currently amended) The [[A]] composition of claim 1, comprising a plurality of siRNA or shRNA molecules ~~the siRNAs or shRNAs of claim 1~~.
79. (Currently amended) The composition of claim 78, wherein at least some of the siRNA or shRNA molecules ~~the siRNAs or shRNAs~~ are targeted to different influenza virus transcripts.
80. (Currently amended) The composition of claim 78, wherein at least some of the siRNA or shRNA molecules ~~the siRNAs or shRNAs~~ are targeted to different regions of the same influenza virus transcript.
81. (Currently amended) The composition of ~~siRNA or shRNA~~ of claim 1, wherein:
delivery of the composition to ~~presence of the siRNA or shRNA within~~ a cell susceptible to influenza virus infection reduces the susceptibility of the cell to infection by at least two influenza strains.
82. (Currently amended) The composition of ~~siRNA or shRNA~~ of claim 1, wherein:
delivery of the composition to ~~presence of the siRNA or shRNA within~~ a subject susceptible to infection with influenza virus reduces the susceptibility of the subject to infection by at least two influenza strains.
83. (Currently amended) A cell comprising the composition ~~siRNA or shRNA~~ of claim 1.
84. (Currently amended) A vector that provides a template for synthesis of the composition ~~siRNA or shRNA~~ of claim 1.
85. (Currently amended) The vector of claim 84, wherein the vector comprises a nucleic acid operably linked to expression signals active in a host cell so that, when the construct is introduced into the host cell, the composition ~~siRNA or shRNA~~ of claim 1 is produced inside the host cell

86. (Currently amended) A vector comprising a nucleic acid operably-linked to expression signals active in a host cell so that, when the construct is introduced into the host cell, that encodes an siRNA or shRNA molecule is produced inside the host cell that is targeted to a transcript of a respiratory virus, an transcript specific to an infectious agent, which transcript is involved in infection by or replication of the agent which molecule comprises (a) a first single-stranded RNA molecule consisting of a sequence that is homologous to highly conserved region of the target transcript among a plurality of variants of the virus and comprises at least 15 consecutive nucleotides, (b) a second singled-stranded molecule that comprises a region that is complementary to the first strand, and (c) an RNA duplex formed by the first and second RNA molecules hybridizing together, wherein the siRNA or shRNA molecule inhibits production of the virus by at least 2 fold, relative to the level that would be present in the absence of the siRNA or shRNA molecule, in cells infected by the virus.
87. (Currently amended) The vector of claim 86, ~~wherein the infectious agent is a virus and~~ wherein multiple variants of the virus exist and wherein the virus is capable of undergoing genetic reassortment or mixing.
88. (Original) A cell comprising the vector of claim 87.
89. (Withdrawn) A transgenic animal comprising the vector of claim 87.
90. (Original) The vector of claim 87, wherein the virus is one whose genome comprises multiple independent nucleic acid molecules.
91. (Currently amended) The vector of claim 87, wherein the respiratory virus ~~infectious agent~~ is an influenza virus.
92. (Currently amended) The vector of claim 91, wherein the siRNA or shRNA molecule ~~vector provides a template for transcription of one or more strands of an siRNA or an shRNA that~~ reduces susceptibility of the cell to infection by influenza virus or inhibits influenza virus production.

93. (Currently amended) The vector of claim 91, wherein the siRNA or shRNA molecule ~~degradation of the target transcript~~ delays, prevents, or inhibits one or more aspects of influenza virus infection or replication.
94. (Currently amended) The vector of claim 92, wherein the sequence of the first strand of the siRNA or shRNA molecule ~~duplex portion~~ is selected from the group consisting of ~~duplex portions~~ of: NP-1496, NP-1496a, PA-2087, PB1-2257, PB1-129, PB2-2240, M-37, and M-598, or a variant of any of the foregoing, wherein the variant differs by at most one nucleotide from the sequence ~~the corresponding siRNA in either its sense portion, antisense portion, or both.~~
95. (Currently amended) The vector of claim 94, wherein the sequence of the first strand of the siRNA or shRNA molecule ~~duplex portion~~ is identical to ~~the duplex portion of~~ NP-1496.
96. (Currently amended) The vector of claim 94, wherein the sequence of the first strand of the siRNA or shRNA molecule ~~duplex portion~~ is identical to ~~the duplex portion of~~ NP-1496a.
97. (Currently amended) The vector of claim 94, wherein the first sense strand ~~or portion~~ of the siRNA or shRNA molecule has a sequence selected from the group consisting of: the first 19 nucleotides of any of SEQ ID NOS: 71, 75, 77, 83, 93, 95, 99, and 188, reading in a 5' to 3' direction.
98. (Original) The vector of claim 86, wherein:
the nucleic acid is operably linked to a promoter for RNA polymerase III.
99. (Original) The vector of claim 98, wherein:
the promoter is a U6 or H1 promoter.
100. (Original) The vector of claim 86, wherein:
the vector is selected from the group consisting of retroviral vectors, lentiviral vectors, adenovirus vectors, and adeno-associated virus vectors.

101. (Original) The vector of claim 86, wherein the vector is a lentiviral vector.
102. (Original) The vector of claim 86, wherein the vector is a DNA vector.
103. (Original) The vector of claim 86, wherein the vector is a virus.
104. (Original) The vector of claim 86, wherein the vector is a lentivirus.
105. (Withdrawn) A method of treating or preventing infection by an infectious agent, the method comprising steps of: administering to a subject prior to, simultaneously with, or after exposure of the subject to the infectious agent, a composition comprising the vector of claim 86 or the cell of claim 88.
106. (Withdrawn) The method of claim 105, wherein the infectious agent is a virus.
107. (Withdrawn) The method of claim 105, wherein the infectious agent infects respiratory epithelial cells.
108. (Withdrawn) The method of claim 105, wherein the infectious agent is an influenza virus.
109. (Withdrawn) The method of claim 105, wherein the composition is administered intravenously.
110. (Withdrawn) The method of claim 105, wherein the composition is administered intranasally.
111. (Withdrawn) The method of claim 105, wherein the composition is administered by inhalation.
112. (Original) A pharmaceutical composition comprising:
the composition of claim 1; and
a pharmaceutically acceptable carrier.
113. (Original) The pharmaceutical composition of claim 112, wherein:
the composition is formulated as an aerosol.

114. (Original) The pharmaceutical composition of claim 112, wherein:
the composition is formulated as a nasal spray.
115. (Original) The pharmaceutical composition of claim 112, wherein:
the composition is formulated for intravenous administration.
116. (Currently amended) The pharmaceutical composition of claim 112, wherein:
the respiratory virus ~~infectious agent~~ is an influenza virus and wherein the
composition further comprises a second anti-influenza agent.
117. (Original) The pharmaceutical composition of claim 116, wherein the second anti-
influenza agent is approved by the United States Food and Drug Administration.
118. (Withdrawn) A method for identifying viral inhibitors, the method comprising steps of:
providing a cell including a candidate siRNA or shRNA whose sequence includes
a region of complementarity with at least one transcript produced during infection with a
virus, which transcript is characterized in that its degradation delays, prevents, or inhibits
one or more aspects of viral infection or replication;
detecting infection by or replication of the virus in the cell; and
identifying an siRNA or shRNA that inhibits viral infectivity or replication, which
siRNA or shRNA is a viral inhibitor.
119. (Withdrawn) The method of claim 118, wherein:
the virus is an influenza virus.
120. (Withdrawn) The method of claim 118, wherein:
the cell is characterized in that in the absence of the siRNA or shRNA the cell
produces at least one viral transcript.
121. (Withdrawn) The method of claim 118, further comprising the step of:
transfecting the cell with a viral genome or infecting the cell with the virus.
122. (Withdrawn) A method of treating or preventing infection by a virus, the method
comprising steps of:

administering to a subject prior to, simultaneously with, or after exposure of the subject to the virus, a composition comprising an effective amount of an RNAi-inducing entity, wherein the RNAi-inducing entity is targeted to a transcript produced during infection by the virus, which transcript is characterized in that reduction in levels of the transcript delays, prevents, or inhibits one or more aspects of infection by or replication of the virus.

123. (Withdrawn) The method of claim 122, wherein:
the virus infects respiratory epithelial cells.
124. (Withdrawn) The method of claim 122, wherein:
the virus is an influenza virus.
125. (Withdrawn) The method of claim 122, wherein the composition is administered into the respiratory tract.
126. (Withdrawn) The method of claim 122, wherein the composition is administered by a conventional intravenous delivery method.
127. (Withdrawn) The method of claim 122, wherein in the absence of the RNAi-inducing entity the virus is able to undergo a complete life cycle leading to production of infectious virus, and wherein the presence of the siRNA or shRNA inhibits production of the virus.
128. (Withdrawn) The method of claim 122, wherein the RNAi-inducing entity comprises a duplex portion selected from the group consisting of: duplex portions of: NP-1496, NP-1496a, PA-2087, PB1-2257, PB1-129, PB2-2240, M-37, and M-598, or a variant of any of the foregoing, wherein the variant differs by at most one nucleotide from the corresponding siRNA in either its sense portion, antisense portion, or both.
129. (Withdrawn) The method of claim 128, wherein the duplex portion is identical to the duplex portion of NP-1496.

130. (Withdrawn) The vector of claim 128, wherein the duplex portion is identical to the duplex portion of NP-1496a.
131. (Withdrawn) A method for designing an siRNA or shRNA having a duplex portion, the method comprising steps of:
- identifying a portion of a target transcript, which portion is highly conserved among a plurality of variants of an infectious agent and comprises at least 15 consecutive nucleotides; and
 - selecting the sequence of the portion as the sequence for the duplex portion of the siRNA or shRNA sense strand or portion.
132. (Withdrawn) The method of claim 131, further comprising:
- selecting a sequence complementary to the portion as the sequence for the duplex portion of the siRNA or shRNA antisense strand or portion.
133. (Withdrawn) The method of claim 132, further comprising:
- adding a 3' overhang to either or both of the sense and antisense strands of the siRNA duplex.
134. (Withdrawn) The method of claim 131, wherein:
- the plurality of variants comprises at least 10 variants.
135. (Withdrawn) The method of claim 131, wherein:
- the plurality of variants comprises at least 15 variants.
136. (Withdrawn) The method of claim 131, wherein:
- the plurality of variants comprises at least 20 variants.
137. (Withdrawn) The method of claim 131, wherein:
- the portion comprises approximately 19 nucleotides.
138. (Withdrawn) The method of claim 131, wherein:
- a portion is considered highly conserved among a plurality of variants if it differs by at most one nucleotide between the variants.

139. (Withdrawn) The method of claim 131, wherein:
the infectious agent is an influenza virus.
140. (Withdrawn) The method of claim 131, wherein:
the infectious agent is capable of undergoing reassortment.
141. (Withdrawn) The method of claim 131, wherein:
the variants include at least two variants, each of which naturally infects a host of
a different species.
142. (Withdrawn) The method of claim 141, wherein:
the species include at least two species selected from the group consisting of
humans, swine, horse, and bird species.
143. (Withdrawn) The method of claim 131, wherein:
the variants include at least two variants, each of which arose in a host of a
different species.
144. (Withdrawn) The method of claim 143, wherein:
the species include at least two species selected from the group consisting of
humans, swine, horse, and bird species.
145. (Currently amended) A composition comprising an siRNA or shRNA ~~designed in
accordance with the method of claim 131~~ molecule produced by a method comprising
steps of:
(a) identifying a sequence of a target transcript that is highly conserved
among a plurality of variants of a respiratory virus and comprises at least 15 consecutive
nucleotides;
(b) synthesizing a first RNA strand comprising the sequence;
(c) synthesizing a second RNA strand comprising a sequence that is
complementary to the first strand;
(d) forming a duplex by combining the first and second strands;
(e) repeating steps (a) through (d) to produce a plurality of siRNA or shRNA
molecules;

(f) testing each siRNA or shRNA molecule from step (e) for its ability to inhibit production of the respiratory virus in a cell infected by the virus; and

(g) identifying a siRNA or shRNA molecule that inhibits at least 2 fold of the virus production.

146. (Withdrawn) A method of reducing or lowering levels of a transcript, which transcript is a vRNA or cRNA, comprising administering an RNAi-inducing entity targeted to an mRNA transcript having a sequence at least a portion of which is complementary to or identical to the vRNA or cRNA transcript.
147. (Withdrawn) A method of inhibiting a first transcript comprising administering an RNAi-inducing entity targeted to a second transcript, wherein inhibition of the second transcript results in inhibition of the first transcript.
148. (Withdrawn) The method of claim 147, wherein the level of the first transcript is reduced relative to its level in the absence of the RNAi-inducing entity.
149. (Withdrawn) The method of claim 147, wherein the level of the second transcript is reduced relative to its level in the absence of the RNAi-inducing entity.
150. (Withdrawn) The method of claim 147, wherein the levels of the first and second transcript are reduced relative to their levels in the absence of the RNAi-inducing entity.
151. (Withdrawn) The method of claim 147, wherein the RNAi-inducing entity is not specifically targeted to the first transcript.
152. (Withdrawn) The method of claim 147, wherein the second transcript encodes a protein that functions in maintaining RNA stability.
153. (Withdrawn) The method of claim 147, wherein the protein is a nucleic acid binding protein.
154. (Withdrawn) The method of claim 153, wherein the nucleic acid binding protein is an RNA binding protein.

155. (Withdrawn) The method of claim 147, wherein the second transcript encodes a polymerase.
156. (Withdrawn) The method of claim 155, wherein the polymerase is an RNA polymerase.
157. (Withdrawn) The method of claim 155, wherein the polymerase is a DNA polymerase.
158. (Withdrawn) The method of claim 155, wherein the polymerase is a reverse transcriptase.
159. (Withdrawn) The method of claim 147, wherein either of both of the first and second transcripts are agent-specific transcripts, wherein the agent is an infectious agent.
160. (Withdrawn) The method of claim 147, wherein the first and second transcripts are agent-specific transcripts, wherein the agent is an infectious agent.
161. (Withdrawn) The method of claim 160, wherein the infectious agent is a virus.
162. (Withdrawn) The method of claim 161, wherein the virus is an influenza virus.
163. (Withdrawn) The method of claim 162, wherein the second transcript encodes either viral NP protein or viral PA protein.
164. (Withdrawn) The method of claim 163, wherein the first transcript encodes a protein selected from the group consisting of: M protein, HA protein, PB1 protein, PB2 protein, or NS protein.
165. (Currently amended) A composition comprising:
an siRNA or shRNA molecule ~~RNAi-inducing entity~~, wherein ~~the molecule the~~
~~RNAi-inducing entity~~ is targeted to an influenza virus transcript, which molecule
comprises (a) a first single-stranded RNA molecule consisting of a sequence that is
homologous to highly conserved region of the target transcript among a plurality of
variants of the virus and comprises at least 15 consecutive nucleotides. (b) a second
singled-stranded molecule that comprises a region that is complementary to the first
strand, and (c) an RNA duplex formed by the first and second RNA molecules

hybridizing together,

wherein the siRNA or shRNA molecule inhibits production of the virus by at least 2 fold, relative to the level that would be present in the absence of the siRNA or shRNA molecule, in cells infected by the virus; and

a delivery agent selected from the group consisting of: cationic polymers, modified cationic polymers, peptide molecular transporters, surfactants suitable for introduction into the lung, neutral or cationic lipids, liposomes, non-cationic polymers, modified non-cationic polymers, bupivacaine, and chloroquine.

166. (Original) The composition of claim 165, wherein the delivery agent comprises a delivery-enhancing moiety to enhance delivery to a cell of interest.
167. (Currently amended) The composition of claim 166 ~~claim 165~~, wherein the delivery-enhancing moiety comprises an antibody, antibody fragment, or ligand that specifically binds to a molecule expressed by the cell of interest.
168. (Original) The composition of claim 167, wherein the cell of interest is a respiratory epithelial cell.
169. (Currently amended) The composition of claim 166 ~~claim 165~~, wherein the delivery-enhancing moiety comprises a moiety selected to reduce degradation, clearance, or nonspecific binding of the delivery agent.
170. (Currently amended) The composition of claim 165, wherein the siRNA or shRNA molecule is produced by RNAi-inducing entity ~~comprises a viral vector~~.
171. (Original) The composition of claim 170, wherein the viral vector comprises a lentiviral vector.
172. (Currently amended) The composition of claim 165, wherein the siRNA or shRNA molecule is produced by RNAi-inducing entity ~~comprises a DNA vector~~.
173. (Currently amended) The composition of claim 165, wherein the siRNA or shRNA molecule is produced by RNAi-inducing entity ~~comprises a virus~~.

174. (Currently amended) The composition of claim 173, wherein the siRNA or shRNA molecule is produced by RNAi-inducing entity comprises a lentivirus.
- 175.-176 (Canceled)
177. (Currently amended) The composition of claim 165, wherein the siRNA or shRNA molecule is produced by RNAi-inducing entity comprises an RNAi-inducing vector whose presence within a cell results in production of an siRNA or shRNA targeted to an influenza virus transcript.
178. (Currently amended) The composition of claim 165, wherein:
the siRNA or shRNA molecule is produced by RNAi-inducing entity comprises an siRNA or shRNA or an RNAi-inducing vector whose presence within a cell results in production of an siRNA or shRNA, wherein the siRNA or shRNA comprises a portion that is perfectly complementary to a region of the target transcript, wherein the portion is at least 15 nucleotides in length.
179. (Currently amended) The composition of claim 165, wherein:
the RNAi-inducing entity comprises an siRNA or shRNA or an RNAi-inducing vector whose presence within a cell results in production of an siRNA or shRNA, wherein the sequence of the first strand of the siRNA or shRNA comprises a sequence duplex portion selected from the group consisting of duplex portions of: NP-1496, NP-1496a, PA-2087, PB1-2257, PB1-129, PB2-2240, M-37, and M-598, or a variant of any of the foregoing, wherein the variant sequence differs by at most one nucleotide from the corresponding sequence of the first strand siRNA or shRNA in either its sense portion, antisense portion, or both.
180. (Currently amended) The composition of claim 179, wherein the first strand sequence siRNA or shRNA duplex portion comprises the duplex portion of NP-1496.
181. (Currently amended) The composition of claim 179, wherein the first strand sequence siRNA or shRNA duplex portion comprises the duplex portion of NP-1496a.

182. (Currently amended) The composition of claim 165, wherein:
the RNAi inducing entity comprises an siRNA or shRNA or an RNAi inducing vector whose presence within a cell results in production of an siRNA or shRNA; wherein the siRNA or shRNA, wherein the sequence of the first sense strand or portion of the siRNA or shRNA comprises a sequence selected from the group consisting of: the first 19 nucleotides of, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 83, SEQ ID NO: 93; SEQ ID NO: 95; SEQ ID NO: 99, and SEQ ID NO: 188 reading in a 5' to 3' direction.
183. (Currently amended) The composition of claim 182, wherein the sequence of the first sense strand or portion of the siRNA or shRNA comprises the sequence of SEQ ID NO: 93.
184. (Currently amended) The composition of claim 182, wherein the sequence of the first sense strand or portion of the siRNA or shRNA comprises the sequence of SEQ ID NO: 188.
185. (Original) The composition of claim 165, wherein the delivery agent is selected from the group consisting of cationic polymers, modified cationic polymers, and surfactants suitable for introduction into the lung.
186. (Original) The composition of claim 185, wherein the cationic polymer is selected from the group consisting of polylysine, polyarginine, polyethyleneimine, polyvinylpyrrolidone, chitosan, and poly(β -amino ester) polymers.
187. (Original) The composition of claim 186, wherein the cationic polymer is polyethyleneimine.
188. (Original) The composition of claim 185, wherein the modified cationic polymer incorporates a modification selected to reduce the cationic nature of the polymer.
189. (Original) The composition of claim 188, wherein the modification comprises substitution with a group selected from the list consisting of: acetyl, imidazole, succinyl, and acyl.

190. (Original) The composition of claim 185, wherein between 25% and 75% of the residues of the modified cationic polymer are modified.
191. (Original) The composition of claim 190, wherein approximately 50% of the residues of the modified cationic polymer are modified.
192. (Original) The composition of claim 185, wherein the delivery agent comprises a surfactant suitable for introduction into the lung.
193. (Original) The composition of claim 192, wherein the surfactant is Infasurf[®], Survanta[®], or Exosurf[®].
194. (Withdrawn) A method of treating or preventing influenza virus replication, pathogenicity, or infectivity comprising administering the composition of claim 165 to a subject at risk of or suffering from influenza virus infection.
195. (Withdrawn) The method of claim 194, wherein the composition is administered by a route selected from the group consisting of: intravenous injection, inhalation, intranasally, and as an aerosol.
196. (Withdrawn) The method of claim 194, wherein the composition is administered intravenously.
197. (Withdrawn) The method of claim 196, wherein the composition is administered using a conventional intravenous administration technique.
198. (Withdrawn) The method of claim 194, wherein the composition is administered by inhalation.
199. (Withdrawn) The method of claim 194, wherein the composition is administered intranasally.
200. (Withdrawn) The method of claim 194, wherein the composition is administered as an aerosol.

201. (Previously presented) A composition comprising:

an siRNA or shRNA targeted to a target transcript of an influenza NP gene, wherein the siRNA or shRNA comprises a core duplex region having sense and antisense strands or portions, wherein the sequence of the sense strand or portion of the core duplex region comprises at least 10 consecutive nucleotides of a target sequence selected from the group consisting of:

nucleotides 3 – 21 of a sequence presented in any of SEQ ID NOs: 1 through 68, with the proviso that either one or two nucleotides among the 19 consecutive nucleotides may differ from that sequence;

nucleotides 1 – 19 of SEQ ID NO: 93, with, optionally, a 3' overhang;

nucleotides 1 – 20 of SEQ ID NO: 188, with, optionally, a 3' overhang; and

nucleotides 1 – 19 of SEQ ID NOs: 93 or 188.